

Perspective

Break-induced replication

What is it and what is it for?

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Abbreviations: HR, homologous recombination; DSB, double-strand break; NHEJ, nonhomologous end joining; DSBR, double-strand-break repair; SDSA, synthesis-dependent strand annealing; BIR, break-induced replication; HJ, holliday junction; CO, crossover; NCO, non crossover; LOH, loss of heterozygosity; GCR, gross chromosome rearrangement

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Homologous recombination (HR) is considered to be an error-free mechanism for the repair of DNA double-strand breaks (DSBs). Indeed, most DSB repair events occur by a non-crossover mechanism limiting loss of heterozygosity (LOH) for markers downstream of the site of repair and preventing chromosome rearrangements. However, DSBs that arise by replication fork collapse or by erosion of uncapped telomeres have only one free end and are thought to repair by strand invasion into a homologous duplex DNA followed by replication to the chromosome end (break-induced replication, BIR). As BIR from one of the two ends of a DSB would result in a long tract of LOH it suggests BIR is suppressed when DSBs have two ends in order for repair to occur by a more conservative HR mechanism. Recent studies showed that BIR can occur by several rounds of strand invasion, DNA synthesis and dissociation resulting in chromosome rearrangements when dissociation and reinvasion occur within dispersed repeated sequences. Thus template switching during BIR can be highly mutagenic and this process could be important for genome evolution and disease development.

Homologous Recombination Pathways

DNA double strand breaks (DSBs) are potentially lethal lesions that occur spontaneously during normal cell metabolism or by treatment of cells with DNA-damaging agents. There are two major pathways to repair DSBs: non-homologous end joining (NHEJ) and homologous recombination (HR). NHEJ involves the religation of the two ends of the broken chromosome and can occur with high fidelity, or be accompanied by gain or loss of nucleotides at the junction.^{1,2} HR relies on the presence of a homologous duplex to template repair of the broken chromosome.³ Several sub-pathways

of HR have been defined; these include DSBR, SDSA and BIR (Fig. 1). BIR is also known as recombination-dependent replication or break-copy duplication.^{4,5} At the molecular level, all three mechanisms are initiated by 5' to 3' degradation of the broken DNA ends to create 3' single-stranded DNA tails.³ Rad51 binds to the resulting single-stranded DNA tails to initiate pairing and strand invasion with homologous duplex DNA. The 3' end from the broken chromosome is used to prime leading strand DNA synthesis templated by the donor duplex. By the canonical DSBR model, the other end of the break interacts with the displaced strand from the donor duplex (D-loop) to prime DNA synthesis and seal the break.⁶ The resulting double HJ intermediate can be resolved to generate crossover (CO) or non-crossover (NCO) products. If the heteroduplex DNA formed during single-strand pairing contains a mismatch, repair of the mismatch can result in gene conversion. During SDSA, the invading strand that has been extended by DNA synthesis is displaced and anneals to complementary sequences exposed by 5'–3' resection of the other side of the break.^{7,8} The remaining gaps can be filled by DNA synthesis and the nicks ligated. Again, mismatch repair can result in gene conversion. Finally, during BIR, a processive replication fork is established after strand invasion and DNA synthesis proceeds to the end of the chromosome.^{5,9} BIR requires leading and lagging strand DNA synthesis, in contrast to SDSA that uses only leading strand DNA synthesis.^{10,11}

HR is generally perceived as a conservative mechanism to repair DSBs in mitotic cells because it preferentially occurs between sister chromatids, leading to genetically silent events. Cohesins, which maintain sister chromatids in close proximity, favor this repair bias versus repair using a homologous chromosome or ectopic repeat.^{12,13} However, mitotic HR can also occur between allelic loci from chromosome homologues. In this situation, DSBR, SDSA and BIR lead to loss of heterozygosity (LOH) if the homologues are polymorphic. While gene conversion (LOH) associated with DSBR and SDSA is limited to a small region surrounding the DSB, gene conversion starts at least at the break site and extends to the end of the chromosome after BIR. It is important to keep in mind that DSBR associated with a CO in the G₂ stage of the cell cycle followed by the co-segregation of parental and recombinant chromatids has the same outcome as BIR

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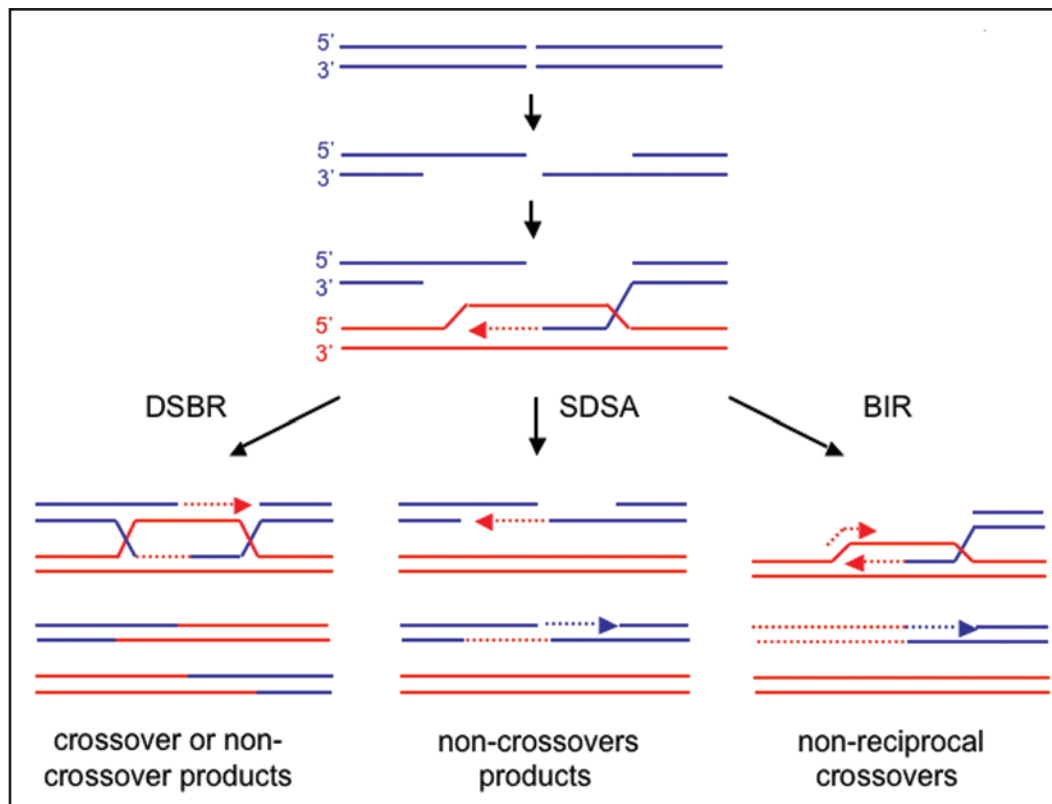


Figure 1. Models for the repair of double-strand breaks. All three mechanisms initiate with invasion of a 3' end. After priming DNA synthesis, the second end is captured and a double Holliday junction intermediate is formed (DSBR). Resolution can occur in either plane at both junctions to generate crossover or non-crossover products. In the SDSA model, the nascent strand is displaced, pairs with the other 3' single-stranded tail and DNA synthesis completes repair. Extensive replication primed from the invading 3' end (BIR) occurs when the other end of the DSB is absent or is heterologous. 3' ends are indicated by arrowheads, newly synthesized DNA is represented by dashed lines.

(Fig. 2). Reducing COs associated with DSBR is one way to prevent long tract LOH. Indeed, COs are associated with only 5–20% of the spontaneous or DSB-induced mitotic gene conversion events in *S. cerevisiae*,^{9,14} and the number of associated COs is even lower in *Drosophila* and mouse cells.^{7,15} Because SDSA is a NCO process this minimizes LOH and appears to be the predominant mechanism for homology-dependent repair of DSBs in mitotic cells.

Physiological Relevance of Break-Induced Replication

The importance of recombination for late replication of bacteriophage T4¹⁶ and in the repair of collapsed replication forks in *Escherichia coli* has been clearly demonstrated.^{4,17} In bacteria replication initiates from a single origin, proceeds bidirectionally, and terminates at a specific region. Collapse of one of the two forks is potentially catastrophic and requires recombination-dependent restart. RecA promotes strand invasion at the collapsed replication fork, but DnaB must be recruited in order for replication to restart. The PriA protein plays a critical role in the recruitment of the DnaB replicative helicase at RecA-catalyzed strand invasion intermediates.^{18,19} In eukaryotes, no PriA homolog or functional equivalent has been identified to date. While it is clear that recombination-dependent replication repair of G₁ and G₂ induced DSBs exists in *S. cerevisiae*,^{5,20,21} and that homologous recombination is required to resume DNA replication in the presence of arrested or stalled forks, the process of recombination-dependent replication restart has not been formally demonstrated.

In eukaryotes, in addition to its putative role to restart collapsed replication forks, BIR is envisioned to elongate telomeres that are lost when telomerase is absent or when telomeres are uncapped.²² The *RAD52* gene, which is required for virtually all homologous recombination events in *S. cerevisiae*, is essential for telomere maintenance in the absence of telomerase.²³ Two sub-pathways have been identified, one involves recombination and amplification of the sub-telomeric Y' repeats; the other results in extensive elongation of the (G₁₋₃T)_n tracts.²² The Y' recombination pathway is *RAD51* dependent and appears similar to other BIR events. The amplification of (G₁₋₃T)_n tracts is independent of *RAD51* and is thought to occur by a rolling circle mechanism using an extrachromosomal circular (G₁₋₃T)_n template. Similar recombination-dependent mechanisms have been proposed for at least some of the telomere elongation events in ALT (alternative lengthening of telomeres) tumors.²⁴

Identifying BIR Events

Because two-ended DSBs are repaired primarily by gene conversion with or without an associated CO, BIR events can only be detected by creating a DSB where just one of the two ends can undergo homology-dependent strand invasion. This can be achieved by inserting a meganuclease cut site between a sequence homologous to a donor site elsewhere in the genome and heterologous sequences, or by using the chromosome fragmentation vector described below.^{5,20,21,25} However, even using these systems it can be difficult to differentiate between half COs formed in G₂ and

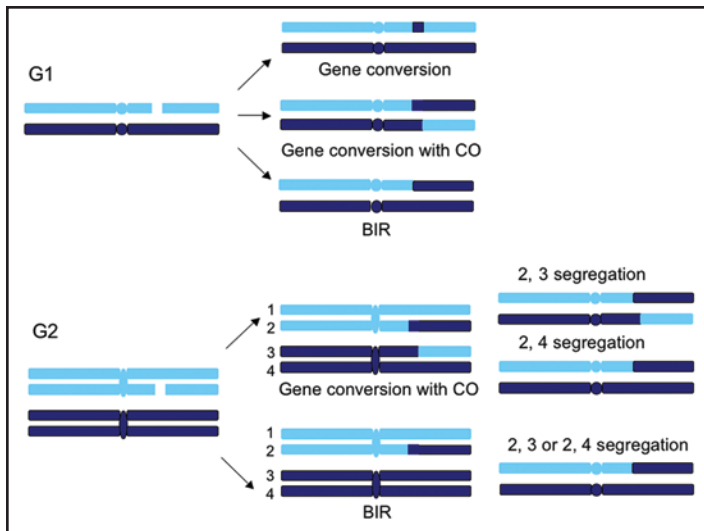


Figure 2. LOH mediated by homologous recombination. The products of DSB repair in G_1 cells are easily distinguished, but BIR and DSB repair associated with crossing over can generate indistinguishable products in G_2 . In G_2 cells, each chromatid is numbered 1 through 4. Depending on how the chromatids segregate (e.g., 2 with 3 or 2 with 4), a reciprocal exchange can generate daughter cells indistinguishable from a BIR event.

BIR because the products can appear the same (Fig. 2). Morrow et al provided compelling evidence that BIR does indeed occur and the events are not due to G_2 COs.⁵ They transformed diploid yeast cells with a linearized chromosome fragmentation vector that has sequences homologous to a unique sequence on yeast chromosome III at one end of the vector and part of the sub-telomeric Y' element at the other end, in addition to a selectable marker, a centromere and origin of replication. A stable chromosome fragment is formed by strand invasion at the chromosome III homology followed by replication to the end of the chromosome arm and strand invasion at a Y' at the other end of the vector to generate a new telomere. Most of the transformed cells retained both copies of chromosome III plus the chromosome fragment. Furthermore, when haploid cells were transformed with a linear vector that had the chromosome III homology at both ends, isochromosome fragments were generated. Two G_2 COs would have deleted the template chromosome arms resulting in inviability and consequently no transformants. Bosco and Haber analyzed the products of BIR following DSB induction in G_1 cells by pedigree analysis and recovered two viable daughter cells each with the expected products from BIR.²⁰ This result is incompatible with a G_2 CO where one daughter cell would be expected to die. Finally, recent experiments from the Haber lab have shown that both leading and lagging strand DNA synthesis machineries are required for BIR, whereas gene conversion requires only leading strand synthesis.^{10,11} The requirement for lagging strand synthesis might be considered a defining feature of BIR.

Current genetic and physical assays for BIR involve repair of the DSB from a non-sister chromatid, a situation that may not be directly relevant to repair of a collapsed replication fork by sister-chromatid recombination. A recently developed plasmid system using a version of the HO endonuclease cut site that is nicked and converted to a DSB during replication may provide a useful system to study repair of a collapsed replication forks via sister chromatid BIR.²⁶

Mechanisms for BIR

The strand invasion step of BIR is assumed to be the same as for gene conversion based on the requirement for the same HR proteins: Rad51, Rad52, Rad54, Rad55 and Rad57.²⁵ However, subsequent steps must be different to account for the low level (<2%) of BIR compared with gene conversion at DSBs with homology on both sides of the break. Physical monitoring has revealed a significant delay in the initiation of DNA synthesis from the invading 3' end during BIR, compared with gene conversion.²¹ Even though the initiation of recombination-dependent replication is slow compared to gene conversion, the kinetics of the DNA synthesis process to produce a fully replicated chromosome arm is similar to that occurring during S-phase.²¹ The delay in initiation of DNA synthesis may reflect a sensing mechanism to detect the other side of the break. After failing to sense the other end, replication initiates and proceeds to the end of the chromosome. An alternate hypothesis for end coordination, or possibly a back-up mechanism to sensing the other end, proposes multiple rounds of dissociation and reinvasion during DSB repair.²⁷ In this model it is suggested that the invading end undergoes limited DNA synthesis and dissociation of the invading strand, as proposed in the SDSA model (Fig. 1), however, if the other end of the break is unavailable for annealing, the extended 3' end undergoes a second round of strand invasion, followed by dissociation and homology searching. This process could be repeated until homology (i.e., the other end of the break) is found and then repair could be completed by SDSA, or in the absence of the other end to pair with, until the end acquires a telomere. The products of gap repair in *Drosophila BLM*^{-/-} mutants and *RAD51*^{-/-} mutants are consistent with the suggestion that repair can involve more than one round of strand invasion.^{28,29} To directly test this model in *S. cerevisiae*, Smith et al., analyzed BIR products recovered from diploid cells with polymorphic chromosome III homologues using the chromosome fragmentation assay.²⁷ Twenty percent of the chromosome fragments analyzed contained sequences derived from both chromosome III homologues consistent with multiple strand invasions (Fig. 3). Furthermore, some of the products were the result of dissociation of the invading strand within a repeated sequence and reinvasion at an ectopic repeat generating a chromosome translocation.

One of the interesting features of the template switching events described by Smith et al.,²⁷ is that they occur over a region of about 10-kb downstream of the site of strand invasion, but do not extend over the entire left arm of chromosome III. There are a number of possible mechanisms that could account for this apparent change in the processivity of BIR. First, it is possible that the strand invasion intermediate is cleaved by a structure-specific nuclease and once the invading strand is covalently joined to one of the template strands the strand invasion process is irreversible (Fig. 4). We consider this to be unlikely because if cleavage of the D-loop occurred during strand invasion then SDSA would be prevented. Furthermore, we have seen no alteration in the frequency of BIR or the distribution of switching events in *mus81* mutants (Smith CE and Symington LS, unpublished). A second possibility is that the invading end from the CFV converges with a replication fork initiated from an origin downstream of the site of strand invasion. Third, there could be a switch between a low processivity polymerase and a high processivity

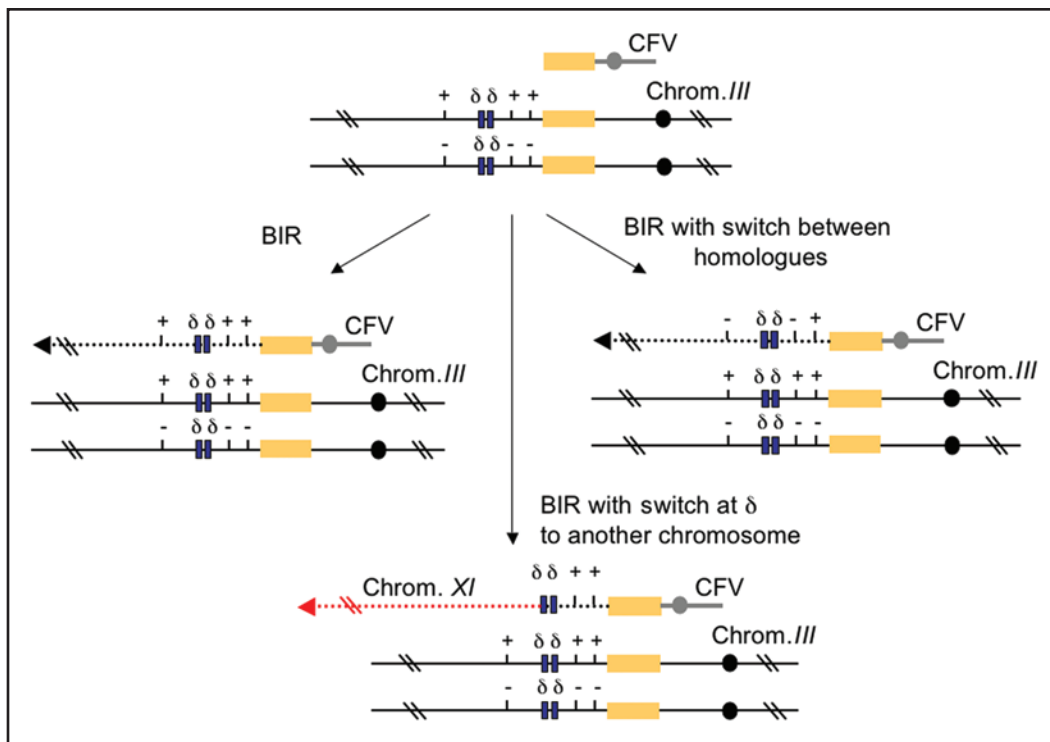


Figure 3. Template switching during BIR. A diploid strain containing restriction site polymorphisms downstream of the site of strand invasion was used to show BIR can occur by more than one strand invasion event. The linear CFV invades one of the two chromosome III homologues, following limited DNA synthesis and dissociation, the second strand invasion could occur into the same homologue or different homologue resulting in the formation of a chimeric chromosome fragment. Dissociation and re-invasion at repeated sequences (δ elements) can result in non-reciprocal translocations. The lightly shaded box represents the region of homology and the filled circles correspond to centromeres.

polymerase during BIR. There is currently no genetic evidence to implicate Pol η or Pol ζ in gene conversion or BIR in budding yeast. However, deletion of *POL η* in chicken DT40 cells reduces the frequency of DSB-induced gene conversion and human POL η has been shown to extend the invading 3' end of D-loop intermediates in vitro.^{30,31} Recent studies by Lydeard et al., have shown a requirement for Pol δ and Pol α to form the initial primer extension product during BIR.¹⁰ Although Pol ϵ is not required for this early step, it is required to complete replication of 30-kb to the end of the chromosome to form a stable chromosome as detected by pulsed-field gel electrophoresis. This raises the intriguing possibility that Pol ϵ might prevent template switching during BIR. Another possibility is that the D-loop formed by strand invasion migrates along the donor duplex as the invading 3' end is extended with the newly synthesized DNA extruded behind the D-loop. This region of single-stranded DNA could be activated for annealing to the other side of the break during SDSA, or for pairing with another duplex DNA to initiate template switching. This scenario would prevent both template switching and SDSA once this DNA becomes double-stranded by initiation of lagging strand synthesis.

A number of interesting mechanistic questions remain regarding the DNA synthesis step of BIR. First, is the replication conservative or semi-conservative? If the D-loop migrates to the end of the chromosome and lagging strand synthesis is initiated on the newly synthesized strand then the products would be conservative, whereas cleavage of the D-loop would be predicted to give rise to semi-conservative products. Second, does lagging strand DNA synthesis proceed as in S-phase or is there just an Okazaki fragment needed to start from the

very end of the completely newly synthesized strand? Third, does BIR require the replicative Mcm helicase complex? If the Mcm complex turns out to be required it would provide support for a restart pathway in eukaryotes.

BIR and GCRs

An intrinsic property of BIR is to produce long tracts of LOH and unbalanced chromosomal aberrations when strand invasion occurs between repeated sequences, usually referred to as gross chromosome rearrangements (GCRs). Formation of spontaneous GCRs is rare, but several methods have been developed to detect these events in yeast. In a systematic screen of LOH events in diploid yeast, the most common class of GCR involved recombination between retrotransposon elements.³² Ty1 is the most common retrotransposon in yeast and is present in 30–40 copies/haploid genome; the solo LTRs (mostly delta elements) are present in about 250 copies.³³ As noted earlier, it is not possible to distinguish between reciprocal exchange between dispersed Ty1 elements and BIR as the underlying mechanism for these rearrangements. Ty or LTR elements feature at the breakpoints of several other types of GCRs in yeast. As described above, template switching between delta elements was detected among 10% of the CF products formed during BIR using the chromosome fragment transformation system.²⁷ This unusually high level of GCRs suggests BIR can be mutagenic. Reducing the levels of Pol α caused chromosome breakage at an inverted duplication of Ty elements that was subsequently repaired by recombination with ectopic Ty elements generating chromosome translocations.³⁴ In another study, a DSB induced 30-kb away from a pair of inverted

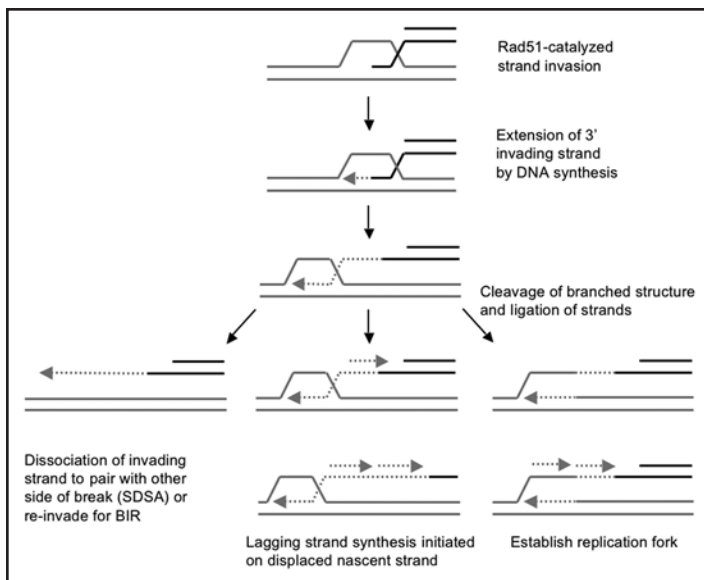


Figure 4. Models for the post-invasion steps of BIR. The invading strand of the strand invasion intermediate is extended by DNA synthesis forming a migrating D-loop. This structure is unstable and can undergo dissociation and reinvasion (left). It is unclear when lagging strand synthesis initiates, but is required to complete replication of the CF. Lagging strand synthesis initiated on the displaced nascent strand results in conservatively replicated products. Alternatively, the strand invasion intermediate could be cleaved by an endonuclease and the strands ligated to covalently link the invading strand to the donor duplex and establish a stable replication fork. Replication would then proceed semi-conservatively.

Ty elements on yeast chromosome III resulted in a burst of genomic instability including translocations between the Ty elements present on chromosome III and ectopic Ty or delta elements.³⁵ Several of these events were complex and could be interpreted as occurring by template switching at Ty or delta elements during BIR.

The frequency of spontaneous rearrangements between Ty elements is about 100 times higher than the non-homology and microhomology-mediated translocations detected in the Kolodner GCR assay.³⁶ In this GCR assay, simultaneous loss of two linked markers located within the non-essential terminal region of chromosome V occurs primarily by breakage and telomere addition or non-reciprocal translocation. Most of the translocation events described are mediated by no homology at the break point or very short sequence homologies and are dependent on *DNL4*, an essential component of the NHEJ pathway.³⁷ In the absence of both *RAD52* and *DNL4* the translocation class of GCRs is eliminated. An unusual class of translocations is detected between highly diverged sequences in the absence of the Sgs1 helicase and at least one other protein involved either in the DNA damage checkpoint response, chromatin assembly or the DNA unwinding.³⁸ Again, many of these translocations were complex because the initial event resulted in formation of dicentric chromosome that underwent a secondary rearrangement to form a stable product. These rearrangements between the diverged *CAN1*, *LYP1* and *ALP1* genes were dependent on *RAD52* and partially dependent on *RAD51*, and the breakpoints were primarily within blocks of greatest sequence identity. Several of the events characterized had multiple breakpoints consistent with their formation by template switching during BIR.

In an assay designed to detect dosage compensation of a single gene, large chromosomal duplications of 41–655 kb were recovered.³⁹ These were mainly intrachromosomal with breakpoint junctions at microsatellites, microhomologies or LTRs. While formation of these events is consistent with BIR, the absence of large homologies at the breakpoints would suggest that if BIR is the underlying mechanism then the homology requirement is lower than for other HR events. Bosco and Haber showed that 72-bp of homology at one side of an HO-induced DSB is sufficient for BIR suggesting small homologies can be used.²⁰ In another study selecting for gene duplications in haploid yeast, the breakpoint junctions for segmental duplications had no homology or microhomologies, and were independent of *RAD52*, suggesting a non-HR mechanism.⁴⁰ Template switching at stalled replication forks has been proposed as a mechanism for gene amplification events in *E. coli* and for copy number changes associated with tandem duplication of the *PLP1* gene in Pelizaeus-Merzbacher disease in humans.^{41–43} These events are proposed to arise by dissociation of the nascent strand at a stalled replication fork and pairing between the primer terminus and the template strand at another replicon via microhomologies. While this model does not necessitate DNA replication be initiated at a DSB, it does suggest very short homologies can be used during template switching. It should also be kept in mind that most of the GCR events analyzed in *S. cerevisiae* occur at very low frequencies and rare events between short homologies may not be detected in standard HR assays, but could be relevant to the duplication of large chromosome segments during evolution and in formation of GCRs associated with human disease.

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